



This is a repository copy of *Genetic overlap between endometriosis and endometrial cancer: evidence from cross-disease genetic correlation and GWAS meta-analyses*.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/138599/>

Version: Published Version

---

**Article:**

Painter, J.N., O'Mara, T.A., Morris, A.P. et al. (73 more authors) (2018) Genetic overlap between endometriosis and endometrial cancer: evidence from cross-disease genetic correlation and GWAS meta-analyses. *Cancer Medicine*, 7 (5). pp. 1978-1987. ISSN 2045-7634

<https://doi.org/10.1002/cam4.1445>

---

**Reuse**

This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here:

<https://creativecommons.org/licenses/>

**Takedown**






If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing [eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk) including the URL of the record and the reason for the withdrawal request.



[eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk)  
<https://eprints.whiterose.ac.uk/>

## ORIGINAL RESEARCH

# Genetic overlap between endometriosis and endometrial cancer: evidence from cross-disease genetic correlation and GWAS meta-analyses

Jodie N. Painter<sup>1</sup> , Tracy A. O'Mara<sup>1</sup>, Andrew P. Morris<sup>2,3</sup>, Timothy H. T. Cheng<sup>4</sup>, Maggie Gorman<sup>4</sup>, Lynn Martin<sup>4</sup>, Shirley Hodson<sup>5</sup>, Angela Jones<sup>4</sup>, Nicholas G. Martin<sup>1</sup>, Scott Gordon<sup>1</sup>, Anjali K. Henders<sup>6</sup>, John Attia<sup>7,8</sup>, Mark McEvoy<sup>8</sup>, Elizabeth G. Holliday<sup>7,8</sup>, Rodney J. Scott<sup>9,10</sup>, Penelope M. Webb<sup>11</sup>, Peter A. Fasching<sup>12,13</sup> , Matthias W. Beckmann<sup>12</sup>, Arif B. Ekici<sup>14</sup>, Alexander Hein<sup>12</sup>, Matthias Rübner<sup>12</sup>, Per Hall<sup>15</sup>, Kamila Czene<sup>15</sup>, Thilo Dörk<sup>16</sup> , Matthias Dürst<sup>17</sup>, Peter Hillemanns<sup>16</sup>, Ingo Runnebaum<sup>17</sup>, Diether Lambrechts<sup>18,19</sup> , Frederic Amant<sup>20</sup>, Daniela Annibaldi<sup>20</sup>, Jeroen Depreeuw<sup>19,20,21</sup>, Adriaan Vanderstichele<sup>20</sup>, Ellen L. Goode<sup>22</sup> , Julie M. Cunningham<sup>23</sup>, Sean C. Dowdy<sup>24</sup>, Stacey J. Winham<sup>22</sup>, Jone Trovik<sup>25,26</sup>, Erling Hoivik<sup>25,26</sup>, Henrica M. J. Werner<sup>25,26</sup>, Camilla Krakstad<sup>25,26</sup>, Katie Ashton<sup>7,10,27</sup>, Geoffrey Otton<sup>28</sup>, Tony Proietto<sup>28</sup>, Emma Tham<sup>29,30</sup>, Miriam Mints<sup>31</sup>, Shahana Ahmed<sup>32</sup>, Catherine S. Healey<sup>32</sup>, Mitul Shah<sup>32</sup>, Paul D. P. Pharoah<sup>32,33</sup>, Alison M. Dunning<sup>32</sup>, Joe Dennis<sup>33</sup>, Manjeet K. Bolla<sup>33</sup>, Kyriaki Michailidou<sup>33,34</sup>, Qin Wang<sup>33</sup>, Jonathan P. Tyrer<sup>32</sup>, John L. Hopper<sup>35</sup>, Julian Peto<sup>36</sup>, Anthony J. Swerdlow<sup>37,38</sup>, Barbara Burwinkel<sup>39,40</sup>, Hermann Brenner<sup>41,42,43</sup>, Alfons Meindl<sup>44</sup>, Hiltrud Brauch<sup>43,45,46</sup>, Annika Lindblom<sup>29</sup>, Jenny Chang-Claude<sup>47,48</sup>, Fergus J. Couch<sup>23</sup>, Graham G. Giles<sup>35,49</sup>, Vessela N. Kristensen<sup>50,51,52</sup>, Angela Cox<sup>53</sup>, Krina T. Zondervan<sup>54</sup>, Dale R. Nyholt<sup>1,55</sup>, Stuart MacGregor<sup>1</sup>, Grant W. Montgomery<sup>1,6</sup>, Ian Tomlinson<sup>4</sup>, Douglas F. Easton<sup>32,33</sup>, Deborah J. Thompson<sup>33</sup> & Amanda B. Spurdle<sup>1</sup>

<sup>1</sup>Department of Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia

<sup>2</sup>Wellcome Trust for Human Genetics, University of Oxford, Oxford, UK

<sup>3</sup>Department of Biostatistics, University of Liverpool, Liverpool, UK

<sup>4</sup>Wellcome Trust Centre for Human Genetics and Oxford NIHR Biomedical Research Centre, University of Oxford, Oxford, UK

<sup>5</sup>Department of Clinical Genetics, St George's, University of London, London, UK

<sup>6</sup>Institute for Molecular Bioscience, University of Queensland, Brisbane, Queensland, Australia

<sup>7</sup>Hunter Medical Research Institute, John Hunter Hospital, Newcastle, New South Wales, Australia

<sup>8</sup>Centre for Clinical Epidemiology and Biostatistics, School of Medicine and Public Health, University of Newcastle, Callaghan, New South Wales, Australia

<sup>9</sup>Division of Molecular Medicine, Pathology North, John Hunter Hospital, Newcastle, New South Wales, Australia

<sup>10</sup>Discipline of Medical Genetics, School of Biomedical Sciences and Pharmacy, Faculty of Health, University of Newcastle, Callaghan, New South Wales, Australia

<sup>11</sup>QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia

<sup>12</sup>Department of Gynaecology and Obstetrics, University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany

<sup>13</sup>David Geffen School of Medicine, Department of Medicine Division of Hematology and Oncology, University of California at Los Angeles, Los Angeles, California

<sup>14</sup>Institute of Human Genetics, University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany

<sup>15</sup>Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

<sup>16</sup>Gynaecology Research Unit, Hannover Medical School, Hannover, Germany

<sup>17</sup>Department of Gynaecology, Jena University Hospital - Friedrich Schiller University, Jena, Germany

<sup>18</sup>VIB Center for Cancer Biology, VIB, Leuven, Belgium

<sup>19</sup>Laboratory for Translational Genetics, Department of Human Genetics, University of Leuven, Leuven, Belgium

<sup>20</sup>Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University Hospitals KU Leuven, University of Leuven, Leuven, Belgium

<sup>21</sup>Vesalius Research Center, VIB, Leuven, Belgium

<sup>22</sup>Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota

<sup>23</sup>Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota

<sup>24</sup>Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Mayo Clinic, Rochester, Minnesota

<sup>25</sup>Centre for Cancer Biomarkers, Department of Clinical Science, University of Bergen, Bergen, Norway

<sup>26</sup>Department of Obstetrics and Gynecology, Haukeland University Hospital, Bergen, Norway

<sup>27</sup>Centre for Information Based Medicine, University of Newcastle, Callaghan, New South Wales, Australia

<sup>28</sup>School of Medicine and Public Health, University of Newcastle, Callaghan, New South Wales, Australia

<sup>29</sup>Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

<sup>30</sup>Clinical Genetics, Karolinska Institutet, Stockholm, Sweden

<sup>31</sup>Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

<sup>32</sup>Department of Oncology, Centre for Cancer Genetic Epidemiology, University of Cambridge, Cambridge, UK

<sup>33</sup>Department of Public Health and Primary Care, Centre for Cancer Genetic Epidemiology, University of Cambridge, Cambridge, UK

<sup>34</sup>Department of Electron Microscopy/Molecular Pathology, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus

<sup>35</sup>Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia

<sup>36</sup>Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

<sup>37</sup>Division of Genetics and Epidemiology, The Institute of Cancer Research, London, UK

<sup>38</sup>Division of Breast Cancer Research, The Institute of Cancer Research, London, UK

<sup>39</sup>Department of Obstetrics and Gynecology, University of Heidelberg, Heidelberg, Germany

<sup>40</sup>Molecular Epidemiology Group, C080, German Cancer Research Center (DKFZ), Heidelberg, Germany

<sup>41</sup>Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany

<sup>42</sup>Division of Preventive Oncology, German Cancer Research Center (DKFZ), National Center for Tumor Diseases (NCT), Heidelberg, Germany

<sup>43</sup>German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany

<sup>44</sup>Division of Gynaecology and Obstetrics, Technische Universität München, Munich, Germany

<sup>45</sup>Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany

<sup>46</sup>University of Tübingen, Tübingen, Germany

<sup>47</sup>Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

<sup>48</sup>Research Group Genetic Cancer Epidemiology, University Cancer Center Hamburg (UCC), University Medical Center Hamburg-Eppendorf, Hamburg, Germany

<sup>49</sup>Cancer Epidemiology & Intelligence Division, Cancer Council Victoria, Melbourne, Victoria, Australia

<sup>50</sup>Department of Cancer Genetics, Institute for Cancer Research, Oslo University Hospital Radiumhospitalet, Oslo, Norway

<sup>51</sup>Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

<sup>52</sup>Department of Clinical Molecular Biology, Oslo University Hospital, University of Oslo, Oslo, Norway

<sup>53</sup>Department of Oncology and Metabolism, Sheffield Institute for Nucleic Acids (SiFoNiA), University of Sheffield, Sheffield, UK

<sup>54</sup>Department of Obstetrics & Gynaecology, Endometriosis CaRe Centre, Nuffield, University of Oxford, Oxford, UK

<sup>55</sup>Institute of Health and Biomedical Innovation and School of Biomedical Science, Queensland University of Technology, Brisbane, Queensland, Australia

## Keywords

Cross-disease analysis, endometrial cancer, endometriosis, genome-wide association study, genetic correlation

## Correspondence

Jodie N. Painter, Department of Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia.

Tel: +61 (0)7 3362 0298; Fax: +61 (0)7 3362 0101;

E-mail: jodie.painter@qimrberghofer.edu.au

## Funding Information

Please refer the acknowledgment section for funding information.

Received: 9 October 2017; Revised: 17

January 2018; Accepted: 21 January 2018

**Cancer Medicine** 2018; 7(5):1978–1987

doi: 10.1002/cam4.1445

## Abstract

Epidemiological, biological, and molecular data suggest links between endometriosis and endometrial cancer, with recent epidemiological studies providing evidence for an association between a previous diagnosis of endometriosis and risk of endometrial cancer. We used genetic data as an alternative approach to investigate shared biological etiology of these two diseases. Genetic correlation analysis of summary level statistics from genomewide association studies (GWAS) using LD Score regression revealed moderate but significant genetic correlation ( $r_g = 0.23$ ,  $P = 9.3 \times 10^{-3}$ ), and SNP effect concordance analysis provided evidence for significant SNP pleiotropy ( $P = 6.0 \times 10^{-3}$ ) and concordance in effect direction ( $P = 2.0 \times 10^{-3}$ ) between the two diseases. Cross-disease GWAS meta-analysis highlighted 13 distinct loci associated at  $P \leq 10^{-5}$  with both endometriosis and endometrial cancer, with one locus (SNP rs2475335) located within *PTPRD* associated at a genomewide significant level ( $P = 4.9 \times 10^{-8}$ , OR = 1.11, 95% CI = 1.07–1.15). *PTPRD* acts in the STAT3 pathway, which has been implicated in both endometriosis and endometrial cancer. This study demonstrates the value of cross-disease genetic analysis to support epidemiological observations and to identify biological pathways of relevance to multiple diseases.

## Introduction

Endometriosis (defined as tissue resembling endometrium in extrauterine sites) and endometrial cancer (cancer of the uterine corpus) are serious gynecological diseases with

major impacts on the quality of life of affected women. Endometriosis is a relatively common disease affecting 6–10% of women of reproductive age and 35–50% of infertile women [1, 2]. Affected women commonly

experience severe menstrual pain, pelvic pain, subfertility or infertility, and bowel-related symptoms. Endometrial cancer is the most common invasive gynecological cancer in Australia, ranking sixth for incident cancers in women [3]. This disease is associated with significant morbidity due to surgery and radiotherapy [4], and treatment is further complicated by the fact that most patients present at relatively older age and with major comorbidities, notably obesity and diabetes. Finding the genes and pathways underlying these complex diseases is an essential step toward developing better diagnostic and therapeutic tools for both diseases. Both diseases are known to have a genetic component, with twin studies showing heritability of endometriosis at ~50% (51%, 95% confidence interval = 33–66% [5];  $H = 47\%$ , 95% CI = 36–57% [6]) and of endometrial cancer 27% (95% CI = 11–43% [7]). Genomewide association studies have, to date, identified 19 independent SNPs as being significantly associated with endometriosis [8] and nine independent SNPs with endometrial cancer [9, 10]. These genomewide-associated SNPs, and the genetic regions in which they occur, are nonoverlapping between the diseases.

Epidemiological, biological, and molecular data all indirectly suggest that there could be links between the two disorders. Endometriosis and endometrial cancer are both hormonally regulated diseases, with increased risk in women exposed to higher levels of estrogen, and decreased or ameliorated risk or symptoms through treatments such as the contraceptive pill and hormonal therapies that include progesterone [11]. Both are associated with increased risk of uterine fibroids [12, 13] and with ovarian cancer: endometriosis through an increased risk of this disease, and endometrial cancer through multiple shared risk factors, and histopathologic and molecular features [14, 15]. Cancer-related genetic changes such as loss of heterozygosity, and altered methylation and expression patterns have been reported for endometriosis [16]. Numerous endometrial cancer-associated genes, including *PTEN* and other genes in the Ingenuity “endometrial cancer pathway,” have been shown to be dysregulated in endometriosis [17, 18].

Epidemiological studies have shown conflicting evidence for a link between a diagnosis of endometriosis and risk of endometrial cancer [13, 19–24]. The interpretation of results from epidemiological studies is complicated by several factors, including small sample sizes, the underdiagnosis and misdiagnosis of endometriosis, inability to adjust for confounders including oral contraceptives and parity, and the exclusion criteria of some epidemiological studies which assumed coincidental diagnosis of endometrial cancer in women ascertained via a diagnosis of endometriosis. For example, Rowlands et al. showed an overall 1.5-fold increased risk of endometrial cancer that was

reduced by excluding cases diagnosed with endometriosis <1 year before the endometrial cancer diagnosis; however, the subset of women with *surgically confirmed* endometriosis diagnosed >1 year prior to cancer showed a significant 2.6-fold increased risk of endometrial cancer [13]. However, a recent study in US nurses which was also able to adjust for diagnosis intervals found no association between either self-reported or laparoscopically confirmed endometriosis and risk of endometrial cancer [22]. Meanwhile, two population-based studies had shown associations between the diseases, although neither was able to adjust for confounders such as parity. A large study including 45,790 Danish women with a clinical diagnosis of endometriosis found increased risks of endometrial cancer >1 year (standardized incidence ratio (SIR) = 1.43, 95% CI = 1.13–1.79) and  $\geq 10$  years (SIR = 1.51, 95% CI = 1.15–1.95) following the endometriosis diagnosis [23]. Another study including 15,488 Taiwanese women diagnosed with endometriosis found a similar link, but only in women diagnosed with endometriosis at over 40 years of age (adjusted hazard ratio = 7.08, 95% CI = 2.33–21.55) [24]. Age-related effects, if present, could have further confounded the results of previous epidemiological studies investigating shared risk of endometriosis and endometrial cancer.

Given the methodological complications inherent in epidemiological studies, unbiased genetic approaches are an ideal way to test for shared biological etiology between endometriosis and disease. For example, a degree of shared genetic etiology has recently been demonstrated between endometriosis and ovarian cancer, including with ovarian cancer subtypes not previously thought to be associated with endometriosis [25]. We used separate genomewide association study (GWAS) datasets for endometriosis and endometrial cancer to estimate the degree to which these two diseases share a common genetic etiology. We then combined these datasets in a cross-disease GWAS meta-analysis to identify genetic loci potentially contributing to the genetic risk of *both* endometriosis and endometrial cancer.

## Materials and Methods

### Genetic overlap between endometriosis and endometrial cancer: datasets and analyses

This study utilized data from four previously published genetic datasets for endometriosis and endometrial cancer (outlined below and in the following section; Table 1) [26–28]. Three of the datasets were GWAS datasets, genotyped using Illumina 610Quad and 670Quad BeadChips (Illumina Inc, San Diego, CA) and containing data for 462,430 SNPs in common between them. Of these, the

**Table 1.** Endometriosis and endometrial cancer datasets utilized in the genetic overlap and genomewide association meta-analyses.

Dataset <sup>1</sup>	Case <i>N</i>	Control <i>N</i>	Genotyping platform	Analysis: Genetic overlap	Meta-analysis
Endometriosis					
QIMR	2270	1870	Illumina 660K	✓	✓
Oxford	924	3460	Illumina 660K	✓	✓
Endometrial cancer					
ANECs	591	1241	Illumina 610K	✓	✓
SEARCH	671	1730	Illumina 610K	✓	✓
NSECG	795	895	Illumina 660K	✓	✓
iCOGS	4402	28,758	Custom Illumina array	—	✓

<sup>1</sup>Further details of the endometrial cancer studies contributing to the various datasets are included in Table S1.

endometriosis GWAS dataset included 3194 Australian (QIMR Berghofer Medical Research Institute (QIMR)) and UK (Oxford) women with surgically confirmed endometriosis as cases [26]. The first endometrial cancer GWAS dataset included 1262 Australian (ANECs) and UK (SEARCH) endometrioid subtype endometrial cancer patients [27], and the second (NSECG) included 795 UK endometrial cancer cases and 895 nonoverlapping controls [28]. All endometrial cancer cases were histologically confirmed to be invasive cancer of the endometrium lining [27]. As previously published, the endometriosis and ANECs-SEARCH endometrial cancer GWAS datasets included the same sets of controls—1870 Australian controls and 5190 UK Wellcome Trust Case Control Consortium (WTCCC) controls. Hence to avoid overlapping control samples in this study, the controls were redistributed as follows: The 1870 Australian controls and two-third of the WTCCC controls ( $n = 3460$ , randomly assigned) were included in the endometriosis GWAS dataset, while an additional set of 1241 Australian controls [28] and the remaining one-third of the WTCCC controls ( $n = 1730$ ) were included in the ANECs-SEARCH endometrial cancer GWAS dataset.

Following quality control [26–28], association analyses were performed for each GWAS dataset using PLINK [29]. Australian and UK cases and controls were analyzed as separate strata within the same GWAS for the endometriosis and ANECs-SEARCH endometrial cancer datasets, adjusting for the first two (endometriosis, ANECs, NSECG) or three (SEARCH) principal components of the genomic kinship matrix [26–28]. The summary results for the ANECs-SEARCH and NSECG datasets were then included in an inverse variance, fixed effects meta-analysis performed using METAL [30], to produce one set of endometrial cancer GWAS results. A fixed effect model was considered more appropriate than a random effect model as our hypothesis is that a proportion of SNPs will be associated with both diseases with the same direction of effect, and a fixed effect model is conservative given no expectation that the effect size is similar. The degree of genetic overlap

between endometriosis and endometrial cancer was then examined using two programs that test the degree of genetic correlation/concordance between diseases using GWAS summary results (individual SNP effect sizes and *P*-values), SNP effect concordance analysis (SECA) [31] and LD Score regression [32].

To account for linkage disequilibrium (LD) between SNPs, SECA employs a “*P*-value informed” SNP clumping procedure to extract a subset of independent SNPs [31] (23,817 SNPs for the current analysis). These SNPs are then partitioned into 12 *P*-value “bins” (e.g.,  $P \leq 0.01$ , 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, and 1.0) for each disease. Using the default settings, a number of binomial and Fisher exact tests were performed on SNPs across all bins ( $12 \times 12$  bins = 144 SNP subset combinations), and on SNP subsets within bins (see Results), to determine the degree to which individual SNPs are concordant in their *P*-value level and direction of effect across two diseases, which can indicate the presence of genetic concordance and SNP pleiotropy [31]. For these analyses, the endometriosis dataset was designated as Dataset 1 and endometrial cancer as Dataset 2.

Taking a different approach, cross-trait LD Score regression utilizes the presence of LD, calculating an LD score between SNPs within a 1 cM window and then regressing the product of the SNP association results (*z* scores) from the two diseases against the LD score [32]. Following the recommendations at <https://github.com/bulik/ldsc/wiki/Heritability-and-Genetic-Correlation>, the “–no-intercept” option was used to constrain the LD Score regression intercept to 0 as there was no sample overlap between the two disease datasets.

### Cross-disease meta-analysis between endometriosis and endometrial cancer

The cross-disease meta-analysis was performed using an inverse variance, fixed effects model in METAL [30] to search for genetic loci potentially contributing to the increased risk of both endometriosis and endometrial



cancer. Heterogeneity was assessed using Cochran's  $Q$ -test. The results for the top SNPs ( $P \leq 10^{-5}$ ) from the endometriosis–endometrial cancer meta-analysis were then compared with results for the same SNPs from the fourth dataset included in this study, a separate, independent sample of 4402 endometrial cancer cases and 28,758 controls genotyped at 211,155 SNPs using a custom Illumina Infinium iSelect array by the Collaborative Oncological Gene-environment Study (“iCOGS”) [33, 34]. SNPs not included on the iCOGS array were imputed (including all SNPs within 1 Mb of the target SNP) using IMPUTE(v2) software [35] and the 1000 Genomes Project (2012 release) as the reference panel [9]. Imputation quality scores ranged from 0.34 to 1.00. Association testing on the iCOGS SNPs was performed using SNPTEST (v2) [36] employing frequentist tests with a logistic regression model adjusting for eight separate strata and the first 10 principal components [9, 28]. These results were then included in the replication meta-analysis, which included all four datasets and was conducted as described for the cross-disease meta-analysis above.

## Results

### Genetic overlap between endometriosis and endometrial cancer

Genetic correlation analyses of GWAS datasets for endometriosis and endometrial cancer revealed the presence of weak to moderate, but significant, genetic overlap between the two diseases. The LD Score regression analysis indicated moderate but significant genetic correlation ( $r_g$ ) between the two diseases ( $r_g = 0.23$ ,  $P = 9.3 \times 10^{-3}$ ). The SECA primary test for the overlap of associated effects, including all 144 SNP subsets, revealed more subsets than expected by chance showing at least nominally significant pleiotropy between endometriosis and endometrial cancer ( $P = 6.0 \times 10^{-3}$ ): The pair of SNP subsets producing the minimum exact binomial test  $P$ -value for pleiotropy (endometriosis SNP subset with  $P \leq 0.002$  and endometrial cancer SNP subset with  $P \leq 0.86$ ) had  $P = 3.3 \times 10^{-4}$ . The primary test for concordant effects between endometriosis and endometrial cancer also revealed that the number of SNP subsets with nominally significant concordant effects ( $P \leq 0.05$ ) was significantly more than expected by chance ( $P = 2.0 \times 10^{-3}$ ): The pair of SNP subsets producing the minimum Fisher's exact test  $P$ -value for effect correlation (endometriosis SNP subset with  $P \leq 0.37$  and endometrial cancer SNP subset with  $P \leq 1$ ) had  $P = 2.1 \times 10^{-4}$ . The primary results indicate that SNP effects are correlated, with the presence of allelic effects that increase the risk of both traits. Including only specific (default) SNP subsets in the analyses [31], SNP

effects were positively, although not significantly, correlated for SNPs at  $P \leq 0.05$  in both datasets ( $P = 8.4 \times 10^{-2}$ ) and for SNPs with  $P \leq 1.0 \times 10^{-5}$  in the larger endometriosis dataset and with  $P \leq 0.05$  in the endometrial cancer dataset ( $P = 6.8 \times 10^{-2}$ ). Together, these results indicate that overall more SNPs than expected by chance were associated with the same direction of effect for both diseases, particularly amongst nominally or marginally associated SNPs.

### Cross-disease genomewide association analyses

For the cross-disease meta-analysis including the endometriosis and endometrial cancer (ANECs-SEARCH and NSECG) GWAS datasets, two SNPs had  $P$ -values reaching genomewide significance (rs6782972,  $P = 3.3 \times 10^{-9}$  and rs2218868,  $P = 4.1 \times 10^{-8}$ ; Table S1). A further 92 SNPs were suggestively ( $P \leq 10^{-5}$ ) associated in the combined analysis of both diseases (Table S1). Following inclusion of the iCOGS association results in the meta-analysis, the  $P$ -values for both rs6782972 and rs2218868 dropped below the threshold for suggestive significance (rs6782972,  $P = 1.2 \times 10^{-2}$ , OR = 0.95, 95% CI = 0.90–0.99; rs2218868,  $P = 1.4 \times 10^{-3}$ , OR = 1.06, 95% CI = 1.02–1.09); hence, neither locus was validated by the endometrial cancer replication dataset. Including all four datasets, 13 loci showed evidence for replication ( $P$ -values  $\leq 10^{-5}$ ; Table 2; Fig. S1), with a genomewide significant signal detected for SNP rs2475335 ( $P = 4.9 \times 10^{-8}$ , OR = 1.11, 95% CI = 1.07–1.14). After adjusting for the multiple testing of 13 SNPs, two SNPs showed evidence of significant heterogeneity between studies (Table 2), rs9865110 ( $P_{\text{het}} = 2.2 \times 10^{-3}$ ) and rs7515106 ( $P_{\text{het}} = 3.6 \times 10^{-3}$ ).

## Discussion

A link between endometriosis and endometrial cancer has long been postulated due to the numerous risk factors shared by the two diseases, but has only recently been convincingly demonstrated epidemiologically [23, 24]. Our genetic study indicates that endometriosis and endometrial cancer have a moderate, but significant, shared genetic etiology. Genetic correlation analyses indicated the presence of pleiotropic SNPs as well as correlation in the direction of genetic effects, particularly amongst SNPs marginally and nominally associated with each disease individually. This is consistent with our hypothesis that a proportion of endometrial cancer cases (but certainly not all) will share genetic predisposition factors in common with endometriosis cases.

Cross-disease meta-analysis identified one genomewide significant locus associated with the risk of developing

**Table 2.** Replicated associations ( $P \leq 10^{-5}$ ) from the cross-disease meta-analysis for endometriosis and endometrial cancer.

Chr	BP	Lead SNP	Flanking gene/ genes <sup>1</sup>	Effect allele	Noneffect allele	GWAS meta-analysis		Replication meta-analysis		$P_{\text{het}}$
						OR (95% CI)	P-value	OR (95% CI)	P-value	
9	10260263	rs2475335	<i>PTPRD</i>	T	C	1.15 (1.09–1.21)	$2.1 \times 10^{-6}$	1.11 (1.07–1.15)	$4.9 \times 10^{-8}$	0.46
3	73981773	rs9865110	<i>PDZRN3-CNTN3</i>	C	A	1.11 (1.06–1.16)	$9.4 \times 10^{-5}$	1.10 (1.06–1.14)	$2.6 \times 10^{-6}$	0.002
17	46262171	rs2278868	<i>SKAP1</i>	C	T	0.87 (0.82–0.93)	$4.7 \times 10^{-7}$	0.92 (0.88–0.96)	$5.5 \times 10^{-6}$	0.05
12	89299016	rs12303900	<i>KITLG-DUSP6</i>	G	T	1.30 (1.17–1.43)	$9.7 \times 10^{-5}$	1.28 (1.17–1.38)	$5.7 \times 10^{-6}$	0.08
6	50715407	rs9349553	<i>TFAP2D</i>	T	C	1.14 (1.08–1.19)	$4.5 \times 10^{-6}$	1.09 (1.05–1.13)	$9.0 \times 10^{-6}$	0.02
4	38765720	rs10008492	<i>KLF3-TLR10</i>	T	C	1.14 (1.08–1.19)	$3.3 \times 10^{-6}$	1.08 (1.05–1.12)	$1.3 \times 10^{-5}$	0.07
13	77164473	rs9530566	<i>LMO7-KCTD12</i>	C	A	1.12 (1.07–1.17)	$3.3 \times 10^{-5}$	1.08 (1.05–1.12)	$1.7 \times 10^{-5}$	0.054
12	4253697	rs10459129	<i>PARP11-CCND2</i>	A	G	0.89 (0.83–0.95)	$6.8 \times 10^{-5}$	0.90 (0.86–0.95)	$2.1 \times 10^{-5}$	0.44
19	31364717	rs2198894	<i>ZNF536-TSHZ3</i>	T	C	1.11 (1.06–1.16)	$8.4 \times 10^{-5}$	1.09 (1.05–1.13)	$2.4 \times 10^{-5}$	0.49
9	32907608	rs7042500	<i>THEM215-APTX</i>	A	G	0.86 (0.79–0.93)	$1.2 \times 10^{-5}$	0.90 (0.86–0.95)	$4.0 \times 10^{-5}$	0.07
17	63665556	rs17693745	<i>CEP112</i>	T	C	1.12 (1.07–1.18)	$2.3 \times 10^{-5}$	1.08 (1.04–1.12)	$5.3 \times 10^{-5}$	0.24
1	22473410	rs7515106	<i>WNT4-ZBTB40</i>	C	T	1.15 (1.08–1.21)	$1.2 \times 10^{-5}$	1.09 (1.04–1.14)	$7.0 \times 10^{-5}$	0.0036
6	57186294	rs1755833	<i>PRIM2</i>	A	G	0.89 (0.84–0.95)	$3.9 \times 10^{-5}$	0.93 (0.89–0.97)	$7.9 \times 10^{-5}$	0.007

<sup>1</sup>Only one gene is listed for SNPs located within genes (introns or exons).

both diseases, and several other loci worthy of prioritization for future studies. These findings indicate that genetic factors underlie at least part of the shared disease risk implied by the epidemiological evidence. The SNP most significantly associated with disease in the endometriosis–endometrial cancer meta-analysis was rs2475335 ( $P = 4.9 \times 10^{-8}$ ). Located on chromosome 9p23, rs2475335 lies within intron 2 of an alternative transcript of the protein tyrosine phosphatase receptor type D (*PTPRD*) gene. *PTPRD* is a member of the receptor protein tyrosine phosphatase (PTP) family, a number of which have been found to function as either tumor suppressors or as oncogenes [37]. *PTPRD* deletions and mutations have been detected in numerous tumor types, including endometrial tumors [38]: the Catalogue of Somatic Mutations in Cancer (COSMIC) database (<http://cancer.sanger.ac.uk/cosmic>; accessed 10/12/2016) indicates ~5% of endometrioid carcinomas harbor *PTPRD* mutations. Mutations in *PTPRD* enhance cell growth and migration in melanoma cell lines, while the presence of mutated *PTPRD* protein enhanced growth and abrogated dephosphorylation of the STAT3 oncoprotein in human astrocytes [38, 39]. Elevated STAT3 expression has been implicated in both endometriosis and endometrial cancer [40, 41] and has been suggested as a potential target for treatment for both diseases [42, 43]. While *PTPRD* is an attractive candidate gene for regulation by rs2475335, the gene targeted by this SNP (or equally by another SNP/s in high linkage disequilibrium with rs2475335) is as yet unknown, and further experimental studies in both endometriosis and endometrial cancer models are now required to investigate the biology underlying the increased risks of both diseases associated with this variant [44].

A number of the remaining risk loci prioritized by the meta-analysis harbor candidate genes that are potentially relevant candidates for etiology and/or treatment of endometriosis and endometrial cancer. For example, the missense variant rs2278868 located on chromosome 17q21.32 within exon 7 of the *SKAP1* gene is in perfect linkage disequilibrium ( $r^2 = 1$ ) with rs1452666, which we have previously reported as having borderline GWAS significant association with endometrial cancer in the combined GWAS and iCOGS datasets [9]. SNP variation in the *SKAP1* region is associated with ovarian cancer, subtypes of which are clearly linked epidemiologically and genetically to endometriosis [25, 45] and to endometrial cancer [46], although rs2278868 is in extremely low LD with the top ovarian cancer SNP rs9303542 ( $r^2 = 0.034$ ) [33]. Publicly available gene expression data (<http://www.gtexportal.org>) indicate the potential for SNPs rs2278868 (and rs1452666) and rs9303542 to act as expression quantitative trait loci (eQTLs) for *SKAP1*, altering *SKAP1* expression in liver, tibial nerve, testis, and pancreatic tissues, as well as for

additional neighboring genes (e.g., *SNX11*, *HOXB2*, and *HOXB3*) in various tissues.

Other SNPs of interest include rs12303900 on chromosome 12q21, located between the *KITLG* and *DUSP6* genes. *DUSP6* is a critical regulator of ERK signaling, a pathway dysregulated in both endometriosis and endometrial cancer and a potential target for treatment for both diseases [47–49]. SNP rs10008492, located on chromosome 4p14, is an eQTL for nearby toll-like receptors *TLR1* and *TLR6* (<http://www.gtexportal.org>). Both *TLR1* and *TLR6* are upregulated in endometriotic mesenchymal stem cells [50] and are expressed in endometrial cancer cell lines [51]. However, as for the *PTPRD* locus, all of these association results need to be further validated in additional replication datasets for both diseases, and relevant functional studies undertaken, before more is hypothesized about their genetic and biological effects on the risk of both endometriosis and endometrial cancer.

In this cross-disease genetic correlation and genomewide association study, we have provided evidence for overlap in genetic risk factors for endometriosis and endometrial cancer. Our genetic correlation analysis supports recent large epidemiological studies indicating an increased risk of endometrial cancer in women previously diagnosed with endometriosis, while the cross-disease meta-analysis has revealed plausible loci that could increase the risk of both diseases and which should be pursued further in functional studies. This work on endometriosis and endometrial cancer also adds further evidence to the utility of cross-disease genetic correlation and GWAS analyses as tractable and attractive methodologies to identify susceptibility loci that predispose to multiple diseases, which could lead to new diagnostic or treatment options for affected individuals.

## Acknowledgments

We acknowledge with appreciation all women who participated in the QIMR Berghofer Medical Research Institute and OXGENE endometriosis studies and the ANECS-SEARCH, NSECG, and iCOGS endometrial cancer studies. For the endometriosis study, we thank Endometriosis Associations for supporting study recruitment, and the many hospital directors and staff, gynecologists, general practitioners, and pathology services in Australia and the UK who provided assistance with blood collection and confirming diagnoses. We are grateful to the many research assistants and interviewers for assistance with the studies contributing to the QIMR and OXGENE collections. The QIMR Study was supported by grants from the National Health and Medical Research Council (NHMRC) of Australia (241944, 339462, 389927, 389875, 389891, 389892, 389938, 443036, 442915, 442981, 496610, 496739, 552485,

and 552498), the Cooperative Research Centre for Discovery of Genes for Common Human Diseases (CRC), Cerylid Biosciences (Melbourne), and donations from Neville and Shirley Hawkins. Genotyping of the OXGENE and QIMR cases was supported by a grant from the Wellcome Trust (WT084766/Z/08/Z) and makes use of WTCCC2 control data generated by the Wellcome Trust Case Control Consortium (full list of investigators at [www.wtccc.org.uk](http://www.wtccc.org.uk)). Funding for the WTCCC project was provided by the Wellcome Trust under award 076113 and 085475. For the endometrial cancer studies, ANECS recruitment was supported by project grants from the NHMRC (339435), Cancer Council Queensland (4196615), and Cancer Council Tasmania (403031 and 457636). The University of Newcastle, the Gladys M. Brawn Senior Research Fellowship scheme, the Vincent Fairfax Family Foundation, the Hunter Medical Research Institute, and the Hunter Area Pathology Service all contributed toward the costs of establishing the control dataset (HCS). SEARCH recruitment was funded by a program grant from Cancer Research UK (C490/A10124). Stage 1 and stage 2 case genotyping was supported by the NHMRC (552402 and 1031333). Control data were generated by the WTCCC, and we acknowledge use of DNA from the British 1958 Birth Cohort collection, funded by UK Medical Research Council grant G0000934 and Wellcome Trust grant 068545/Z/02; funding for this project was provided by the Wellcome Trust under award 085475. NSECG case recruitment was supported by the European Union's Framework Programme 7 CHIBCHA grant and Wellcome Trust Centre for Human Genetics Core Grant 090532/Z/09Z, and control (CORGI) recruitment by Cancer Research UK. The iCOGS endometrial cancer analysis was supported by an NHMRC project grant (1031333). Funding for iCOGS infrastructure came from the European Community's Seventh Framework Programme under grant agreement 223175 (HEALTH-F2-2009-223175) (COGS), Cancer Research UK (C1287/A10118, C1287/A10710, C12292/A11174, C1281/A12014, C5047/A8384, C5047/A15007, C5047/A10692, and C8197/A16565), the US National Institutes of Health (R01 CA128978, U19 CA148537, U19 CA148065, and U19 CA148112), the US Department of Defense (W81XWH-10-1-0341), and the Canadian Institutes of Health Research (CIHR) for the CIHR Team in Familial Risks of Breast Cancer, the Susan G. Komen Foundation for the Cure, the Breast Cancer Research Foundation, and the Ovarian Cancer Research Fund. The Bavarian Endometrial Cancer Study (BECS) was partly funded by the ELAN fund of the University of Erlangen. The Hannover–Jena Endometrial Cancer Study was partly supported by the Rudolf Bartling Foundation. The Leuven Endometrium Study (LES) was supported by the Verelst Foundation for Endometrial Cancer. The Mayo



Endometrial Cancer Study (MECS) and Mayo controls (MAY) were supported by grants from the National Cancer Institute of the US Public Health Service (R01 CA122443, P30 CA15083, and P50 CA136393), the Fred C. and Katherine B. Andersen Foundation, the Mayo Foundation, and the Ovarian Cancer Research Fund with support of the Smith family, in memory of Kathryn Sladek Smith. MoMaTEC received financial support from a Helse Vest Grant, the University of Bergen, the Melzer Foundation, the Norwegian Cancer Society (Harald Andersens legat), the Research Council of Norway, and Haukeland University Hospital. The Newcastle Endometrial Cancer Study (NECS) acknowledges contributions from the University of Newcastle, the NBN Children's Cancer Research Group, and Jennie Thomas and the Hunter Medical Research Institute. RENDOCAS was supported through the regional agreement on medical training and clinical research (ALF) between the Stockholm County Council and Karolinska Institutet (20110222, 20110483, 20110141, and DF 07015), Swedish Labor Market Insurance (100069), and the Swedish Cancer Society (11 0439). The Cancer Hormone Replacement Epidemiology in Sweden study (CAHRES; formerly called the Singapore and Swedish Breast/Endometrial Cancer study, SASBAC) was supported by funding from the Agency for Science, Technology and Research of Singapore (A\*STAR), the US National Institutes of Health, and the Susan G. Komen Breast Cancer Foundation. For the iCOG controls, BCAC is funded by Cancer Research UK (C1287/A10118 and C1287/A12014). OCAC is supported by a grant from the Ovarian Cancer Research Fund thanks to donations by the family and friends of Kathryn Sladek Smith (PPD/RPCI.07) and the UK National Institute for Health Research Biomedical Research Centres at the University of Cambridge. The Australian Breast Cancer Family Study (ABCFS) was supported by grant UM1 CA164920 from the National Cancer Institute (USA). The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the Breast Cancer Family Registry (BCFR), nor does mention of trade names, commercial products, or organizations imply endorsement by the USA Government or the BCFR. The ABCFS was also supported by the National Health and Medical Research Council of Australia, the New South Wales Cancer Council, the Victorian Health Promotion Foundation (Australia) and the Victorian Breast Cancer Research Consortium. The AOCS gratefully acknowledge the cooperation of the participating institutions in Australia and also acknowledge the contribution of the study nurses, research assistants, and all clinical and scientific collaborators. A complete list of the AOCS Study Group can be found at [www.aocstudy.org](http://www.aocstudy.org). AOCS was supported by the U.S. Army Medical Research and Materiel Command under

DAMD17-01-1-0729, The Cancer Council Victoria, Queensland Cancer Fund, The Cancer Council New South Wales, The Cancer Council South Australia, The Cancer Foundation of Western Australia, The Cancer Council Tasmania, and the National Health and Medical Research Council of Australia (NHMRC; ID400413, ID400281). The AOCS gratefully acknowledges additional support from Ovarian Cancer Australia and the Peter MacCallum Foundation. ABS and JLH are supported by NHMRC Senior Research Fellowships. TOM is supported by an NHMRC Early Career Fellowship. GWM is supported by an NHMRC Principal Research Fellowship. APM is supported by a Wellcome Senior Fellowship in Basic Biomedical Science. SM is supported by an Australian Research Council Fellowship. The Cox research group is supported by the Sheffield Experimental Cancer Medicine Centre and Breast Cancer Now.

## Conflict of Interest

None declared.

## References

1. Burney, R. O., and L. C. Giudice. 2012. Pathogenesis and pathophysiology of endometriosis. *Fertil. Steril.* 98:511–519.
2. Meuleman, C., B. Vandenabeele, S. Fieuws, C. Spiessens, D. Timmerman, and T. D'Hooghe. 2009. High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners. *Fertil. Steril.* 92:68–74.
3. Australian Institute of Health and Welfare (AIHW) & Australasian Association of Cancer Registries (AACR). 2004. *Cancer in Australia 2001*. AIHW cat. no. CAN 23. Canberra: AIHW (Cancer Series no. 28).
4. Varol, N., M. Healey, P. Tang, P. Sheehan, P. Maher, and D. Hill. 2001. Ten-year review of hysterectomy morbidity and mortality: can we change direction? *Aust. N. Z. J. Obstet. Gynaecol.* 41:295–302.
5. Treloar, S. A., D. T. O'Connor, V. M. O'Connor, and N. G. Martin. 1999. Genetic influences on endometriosis in an Australian twin sample. *Fertil. Steril.* 71:701–710.
6. Saha, R., H. J. Pettersson, P. Svedberg, M. Olovsson, A. Bergqvist, L. Marions, et al. 2015. Heritability of endometriosis. *Fertil. Steril.* 104:947–952.
7. Mucci, L. A., J. B. Hjelmborg, J. R. Harris, K. Czene, D. J. Havelick, T. Scheike, et al. 2016. Familial risk and heritability of cancer among twins in Nordic countries. *JAMA* 315:68–76.
8. Sapkota, Y., V. Steinhorsdottir, A. P. Morris, A. Fassbender, N. Rahmioglu, I. De Vivo, et al. 2017. Meta-analysis identifies five novel loci associated with

- endometriosis highlighting key genes involved in hormone metabolism. *Nat. Commun.* 8:15539.
9. Cheng, T. H., D. J. Thompson, T. A. O'Mara, J. N. Painter, D. M. Glubb, S. Flach, et al. 2016. Five endometrial cancer risk loci identified through genome-wide association analysis. *Nat. Genet.* 48:667–674.
  10. Chen, M. M., T. A. O'Mara, D. J. Thompson, J. N. Painter, Australian National Endometrial Cancer Study Group, J. Attia, et al. 2016. GWAS meta-analysis of 16 852 women identifies new susceptibility locus for endometrial cancer. *Hum. Mol. Genet.* 25:2612–2620.
  11. Wetendorf, M., and F. J. DeMayo. 2012. The progesterone receptor regulates implantation, decidualization, and glandular development via a complex paracrine signaling network. *Mol. Cell. Endocrinol.* 357:108–118.
  12. Uimari, O., I. Jarvela, and M. Ryyanen. 2011. Do symptomatic endometriosis and uterine fibroids appear together? *J. Hum. Reprod. Sci.* 4:34–38.
  13. Rowlands, I. J., C. M. Nagle, A. B. Spurdle, P. M. Webb, and Australian National Endometrial Cancer Study Group, Australian Ovarian Cancer Study Group. 2011. Gynecological conditions and the risk of endometrial cancer. *Gynecol. Oncol.* 123:537–541.
  14. Munksgaard, P. S., and J. Blaakaer. 2012. The association between endometriosis and ovarian cancer: a review of histological, genetic and molecular alterations. *Gynecol. Oncol.* 124:164–169.
  15. Merritt, M. A., and D. W. Cramer. 2010. Molecular pathogenesis of endometrial and ovarian cancer. *Cancer Biomark.* 9:287–305.
  16. Kokcu, A. 2011. Relationship between endometriosis and cancer from current perspective. *Arch. Gynecol. Obstet.* 284:1473–1479.
  17. Aghajanova, L., and L. C. Giudice. 2011. Molecular evidence for differences in endometrium in severe versus mild endometriosis. *Reprod. Sci.* 18:229–251.
  18. Dentillo, D. B., J. Meola, R. A. Ferriani, and E. S. J. C. Rosa. 2016. Common dysregulated genes in endometriosis and malignancies. *Rev. Bras. Ginecol. Obstet.* 38:253–262.
  19. Brinton, L. A., G. Gridley, I. Persson, J. Baron, and A. Bergqvist. 1997. Cancer risk after a hospital discharge diagnosis of endometriosis. *Am. J. Obstet. Gynecol.* 176:572–579.
  20. Brinton, L. A., L. C. Sakoda, M. E. Sherman, K. Frederiksen, S. K. Kjaer, B. I. Graubard, et al. 2005. Relationship of benign gynecologic diseases to subsequent risk of ovarian and uterine tumors. *Cancer Epidemiol. Biomarkers Prev.* 14:2929–2935.
  21. Olson, J. E., J. R. Cerhan, C. A. Janney, K. E. Anderson, C. M. Vachon, and T. A. Sellers. 2002. Postmenopausal cancer risk after self-reported endometriosis diagnosis in the Iowa Women's Health Study. *Cancer* 94:1612–1618.
  22. Poole, E. M., W. T. Lin, M. Kvaskoff, Vivo I. De, K. L. Terry, and S. A. Missmer. 2017. Endometriosis and risk of ovarian and endometrial cancers in a large prospective cohort of U.S. nurses. *Cancer Causes Control* 28:437–445.
  23. Mogensen, J. B., S. K. Kjaer, L. Møllekjær, and A. Jensen. 2016. Endometriosis and risks for ovarian, endometrial and breast cancers: a nationwide cohort study. *Gynecol. Oncol.* 143:87–92.
  24. Yu, H.-C., C.-Y. Lin, W.-C. Chang, B.-J. Shen, W.-P. Chang, and C.-M. Chuang. 2015. Increased association between endometriosis and endometrial cancer: a nationwide population-based retrospective cohort study. *Int. J. Gynecol. Cancer* 25:447–452.
  25. Lu, Y., G. Cuellar-Partida, J. N. Painter, D. R. Nyholt, Australian Ovarian Cancer Study, International Endogene Consortium, et al. 2015. Shared genetics underlying epidemiological association between endometriosis and ovarian cancer. *Hum. Mol. Genet.* 24:5955–5964.
  26. Painter, J. N., C. A. Anderson, D. R. Nyholt, S. Macgregor, J. Lin, S. H. Lee, et al. 2011. Genome-wide association study identifies a locus at 7p15.2 associated with endometriosis. *Nat. Genet.* 43:51–54.
  27. Spurdle, A. B., D. J. Thompson, S. Ahmed, K. Ferguson, C. S. Healey, T. O'Mara, et al. 2011. Genome-wide association study identifies a common variant associated with risk of endometrial cancer. *Nat. Genet.* 43:451–454.
  28. Painter, J. N., T. A. O'Mara, J. Batra, T. Cheng, F. A. Lose, J. Dennis, et al. 2015. Fine-mapping of the HNF1B multicancer locus identifies candidate variants that mediate endometrial cancer risk. *Hum. Mol. Genet.* 24:1478–1492.
  29. Purcell, S., B. Neale, K. Todd-Brown, L. Thomas, M. A. Ferreira, D. Bender, et al. 2007. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am. J. Hum. Genet.* 81:559–575.
  30. Willer, C. J., Y. Li, and G. R. Abecasis. 2010. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* 26:2190–2191.
  31. Nyholt, D. R. 2014. SECA: SNP effect concordance analysis using genome-wide association summary results. *Bioinformatics* 30:2086–2088.
  32. Bulik-Sullivan, B. K., P. R. Loh, H. K. Finucane, S. Ripke, J. Yang, Schizophrenia Working Group of the Psychiatric Genomics, et al. 2015. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* 47:291–295.
  33. Pharoah, P. D., Y. Y. Tsai, S. J. Ramus, C. M. Phelan, E. L. Goode, K. Lawrenson, et al. 2013. GWAS meta-analysis and replication identifies three new

- susceptibility loci for ovarian cancer. *Nat. Genet.* 45:362–370, 70e1–2.
34. Michailidou, K., P. Hall, A. Gonzalez-Neira, M. Ghoussaini, J. Dennis, R. L. Milne, et al. 2013. Large-scale genotyping identifies 41 new loci associated with breast cancer risk. *Nat. Genet.* 45:353–361, 61e1–2.
  35. Howie, B., J. Marchini, and M. Stephens. 2011. Genotype imputation with thousands of genomes. *G3: Genes - Genomes - Genetics* 1:457–470.
  36. Marchini, J., B. Howie, S. Myers, G. McVean, and P. Donnelly. 2007. A new multipoint method for genome-wide association studies by imputation of genotypes. *Nat. Genet.* 39:906–913.
  37. Zhao, S., D. Sedwick, and Z. Wang. 2015. Genetic alterations of protein tyrosine phosphatases in human cancers. *Oncogene* 34:3885–3894.
  38. Walia, V., T. D. Prickett, J. S. Kim, J. J. Gartner, J. C. Lin, M. Zhou, et al. 2014. Mutational and functional analysis of the tumor-suppressor PTPRD in human melanoma. *Hum. Mutat.* 35:1301–1310.
  39. Veeriah, S., C. Brennan, S. Meng, B. Singh, J. A. Fagin, D. B. Solit, et al. 2009. The tyrosine phosphatase PTPRD is a tumor suppressor that is frequently inactivated and mutated in glioblastoma and other human cancers. *Proc. Natl. Acad. Sci. U S A.* 106:9435–9440.
  40. Kim, B. G., J. Y. Yoo, T. H. Kim, J. H. Shin, J. F. Langenheim, S. D. Ferguson, et al. 2015. Aberrant activation of signal transducer and activator of transcription-3 (STAT3) signaling in endometriosis. *Hum. Reprod.* 30:1069–1078.
  41. Chen, C. L., F. C. Hsieh, J. C. Lieblein, J. Brown, C. Chan, J. A. Wallace, et al. 2007. Stat3 activation in human endometrial and cervical cancers. *Br. J. Cancer* 96:591–599.
  42. Prather, G. R., J. A. 2nd MacLean, M. Shi, D. K. Boadu, M. Paquet, and K. Hayashi. 2016. Niclosamide as a potential nonsteroidal therapy for endometriosis that preserves reproductive function in an experimental mouse model. *Biol. Reprod.* 95:76.
  43. van der Zee, M., A. Sacchetti, M. Cansoy, R. Joosten, M. Teeuwssen, C. Heijmans-Antonissen, et al. 2015. IL6/JAK1/STAT3 Signaling Blockade in Endometrial Cancer Affects the ALDHhi/CD126 + Stem-like Component and Reduces Tumor Burden. *Cancer Res.* 75:3608–3622.
  44. Edwards, S. L., J. Beesley, J. D. French, and A. M. Dunning. 2013. Beyond GWASs: illuminating the dark road from association to function. *Am. J. Hum. Genet.* 93:779–797.
  45. Pearce, C. L., C. Templeman, M. A. Rossing, A. Lee, A. M. Near, P. M. Webb, et al. 2012. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. *Lancet Oncol.* 13:385–394.
  46. Cramer, D. W. 2012. The epidemiology of endometrial and ovarian cancer. *Hematol. Oncol. Clin. North Am.* 26:1–12.
  47. McKinnon, B. D., V. Kocbek, K. Nirgianakis, N. A. Bersinger, and M. D. Mueller. 2016. Kinase signalling pathways in endometriosis: potential targets for non-hormonal therapeutics. *Hum. Reprod Update* 22:pii: dmV060.
  48. Kim, T. H., J. Y. Yoo, H. I. Kim, J. Gilbert, B. J. Ku, J. Li, et al. 2014. Mig-6 suppresses endometrial cancer associated with Pten deficiency and ERK activation. *Cancer Res.* 74:7371–7382.
  49. Westin, S. N., and R. R. Broaddus. 2012. Personalized therapy in endometrial cancer: challenges and opportunities. *Cancer Biol. Ther.* 13:1–13.
  50. Koipallil Gopalakrishnan Nair, A. R., H. Pandit, N. Warty, and T. Madan. 2015. Endometriotic mesenchymal stem cells exhibit a distinct immune phenotype. *Int. Immunol.* 27:195–204.
  51. Aboussahoud, W., R. Aflatoonian, C. Bruce, S. Elliott, J. Ward, S. Newton, et al. 2010. Expression and function of Toll-like receptors in human endometrial epithelial cell lines. *J. Reprod. Immunol.* 84:41–51.

## Supporting Information

Additional supporting information may be found in the online version of this article:

**Figure S1.** Forest plots of association between the top 13 SNPs in the endometriosis-endometrial cancer meta-analysis and each of the datasets included in the analysis.

**Table S1.** Results for the top SNPs from the endometriosis and endometrial cancer (ANES-SEARCH and NSECG) GWAS meta-analysis, with iCOGS as the endometrial cancer replication dataset.